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Diastereoselective synthesis of *syn*-3,5-dihydroxyesters via ruthenium-catalyzed asymmetric transfer hydrogenation

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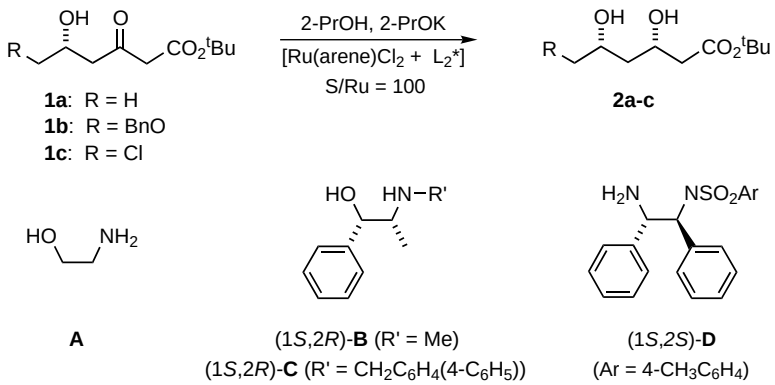
Abstract—The asymmetric transfer hydrogenation of chiral 5-hydroxy-3-ketoesters in 2-propanol using chlororuthenium(II)arene/β-amino alcohol in situ catalyst combinations or a pre-synthesized Ru-{β-amino alcohol} true catalyst, provides *syn*-3,5-dihydroxyesters in high yields and up to 80% de.

syn-3,5-Dihydroxyesters **2** are advanced building blocks for the preparation of mevinic-type HMG-CoA reductase inhibitors of industrial interest,[1] such as compactin[2] and mevinolin.[3] Their current synthesis implies the *syn*-diastereoselective reduction of optically pure aldols, i.e. 5-hydroxy-3-ketoesters **1**, with the $NaBH_4/BEt_3$ or $NaBH_4/B(OMe)_2Et$ combinations.[1,4] This method must, however, be performed at low temperature ($\leq -60°C$) to reach high stereoselectivity and uses expensive borane stoichiometric reagents that generate considerable amounts of waste. It is therefore of great interest to develop efficient *catalytic* approaches toward these key intermediates that proceed under friendly conditions. Previous efforts in this direction by Saburi and our group aimed at the ruthenium-catalyzed asymmetric one-pot hydrogenation (H_2) of 3,5-diketoesters have shown that the *anti*-diol is the favoured stereoisomer in this process.[5,6] Herein we report that the ruthenium-catalyzed asymmetric transfer hydrogenation of 2-propanol[7–11] to chiral 5-hydroxy-3-ketoesters provides an effective entry to *syn*-3,5-dihydroxyesters in high yields and promising diastereoselectivity (Scheme 1, Table 1).

tert-Butyl (*S*)-5-hydroxy-3-oxohexanoate (**1a**) was chosen as a model substrate for preliminary investigations. The treatment of **1a** with the in situ catalytic combination of $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ and ethanolamine[11] (**A**) (1:4) in 2-propanol in the presence of 6 equiv. (versus Ru) of 2-PrOK at 50°C for 25 h gave diol **2a** in high chemoselectivity but poor conversion (entry 1). ^1H and ^{13}C NMR analysis of **2a** and GLC analysis of the



Scheme 1.

Keywords: asymmetric transfer hydrogenation; *syn*-diols; chiral Ru catalysts.
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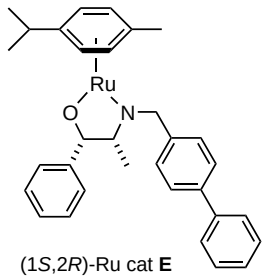
Table 1. Ruthenium-catalyzed asymmetric transfer hydrogenation of aldols **1a**,**b** in 2-propanol[a]

Entry	Aldol **1a–c**	Precursor Ru arene	Ligand	Temp. (°C)	Time (min)	Conv. **1** (mol%)	Sel. **2** (mol%)	de **2** (%)
1	(*S*)-**1a**	*p*-Cymene	**A**	50	1500	29	>98	12 *syn*
2	(*S*)-**1a**	Benzene	(1*R*,2*S*)-**B**	50	20	99	97	25 *anti*
3	(*S*)-**1a**	Benzene	(1*S*,2*R*)-**B**	50	10	75	>98	66 *syn*
					60	100	78	46 *syn*
4	(*S*)-**1a**	Benzene	(1*S*,2*R*)-**B**	20	1140	85	>98	70 *syn*
					1560	98	>98	66 *syn*
5	(*S*)-**1a**	*p*-Cymene	(1*R*,2*S*)-**B**	50	60	87	>98	44 *anti*
6	(*S*)-**1a**	*p*-Cymene	(1*S*,2*R*)-**B**	50	60	96	97	71 *syn*
7	(*S*)-**1a**	*p*-Cymene	(1*S*,2*R*)-**B**	20	1860	79	>98	79 *syn*
					3660	100	91	73 *syn*
8	(*S*)-**1a**	*p*-Cymene	(1*S*,2*R*)-**B**	80	15	90	>98	74 *syn*
					20	99	95	60 *syn*
9	(*S*)-**1a**	Anisole	(1*S*,2*R*)-**B**	50	80	78	>98	72 *syn*
10	(*S*)-**1a**	*t*Bu-benzene	(1*S*,2*R*)-**B**	50	2880	48	>98	39 *anti*
11	(*S*)-**1a**	Benzene	(1*S*,2*R*)-**C**	50	60	67	>98	70 *syn*
					90	95	94	65 *syn*
12	(*S*)-**1a**	*p*-Cymene	(1*S*,2*R*)-**C**	50	60	29	>98	80 *syn*
					1320	47	>98	70 *syn*
13[b]	(*S*)-**1a**	(1*S*,2*R*)-Ru **E**		20	90	86	>98	75 *syn*
					450	98	97	72 *syn*
14	(*S*)-**1a**	*p*-Cymene	(1*S*,2*S*)-**D**	50	90	78	>98	14 *anti*
					1380	98	86	10 *anti*
15	(*S*)-**1a**	*p*-Cymene	(1*R*,2*R*)-**D**	50	240	>99	89	15 *syn*
				30	120	50	>98	72 *syn*
16	(*R*)-**1b**	*p*-Cymene	(1*S*,2*R*)-**B**		1440	>98	86	68 *syn*

[a] The reaction was carried out using 2.0 mmol of **1** and 0.02 mmol of Ru in a 0.1 M 2-propanol solution. See footnote † for a typical procedure.
[b] Reaction carried out with isolated catalyst; see Ref. 11.

corresponding acetonide[10] showed a low de in favour of the *syn* diastereomer. This indicates a limited induction of the chiral centre present in the substrate. When the same reaction was performed with catalytic combinations based on ephedrine derivatives (**B**, **C**), a significant increase in the reduction rate was observed. Completion was usually reached within 1 h at 50°C in the presence of 1 mol% of Ru. Consistent with the above results, reversing the configuration of the chiral ligand resulted in opposite diastereoselectivity for the diols. *syn*-Diol **2a** is formed from (+)-(1*S*,2*R*)-ephedrine type ligands which give the 'match-pair', considering that the de values with these ligands are systematically higher than those observed from systems based on (−)-(1*R*,2*S*)-ephedrine type ligands (compare entries 2/3 and 5/6). Previous work in the field of ruthenium-catalyzed asymmetric transfer hydrogenation of ketones has highlighted the importance of both the chiral ligand *and* arene ligand on the enantioselectivity and activity of the reaction.[8–11] This also proved to be the case in the present application. With respect to the influence of the arene ligand, the Ru–benzene precursor gave, under the same reaction conditions, more active but less stereoselective catalysts than those based on the commonly used Ru–(*p*-cymene) precursor (entries 2/5, 3/6, 4/7, 11/12); reduced steric hindrance at the catalytically active metal center for the Ru-benzene system most likely accounts for this very general trend. Using the same arguments, one may reasonably rationalize: (i) the similar performance of the Ru–anisole and Ru–(*p*-cymene) systems (entries 6/9), and (ii) the extreme sluggishness of the Ru–(*t*butyl-benzene) and the marked reverse in the diastereoselectivity of the reaction[10] from *syn* to *anti* with this system compared to the other Ru–arene catalysts investigated (entry 10). The latter experiment clearly confirms a catalyst-control of the stereoselectivity of the reduction. Regarding the chiral ligand, systems based on Noyori's TsDPEN (**D**)[8] proved surprisingly inefficient in terms of stereoselectivity, no matter what the ligand configuration (entries 14 and 15). *N*-4-(Biphenyl)methyl-norephedrine (**C**), that we specifically developed for the asymmetric transfer hydrogenation of functionalized ketones such as β-keto esters,[10] did not bring in this case a significant enhancement of the diastereoselectivity compared to systems based on simple ephedrine (**B**), but led logically to decreased reaction rates (entries 3/11, 6/12). All in all, the best compromise between stereoselectivity and activity for the reduction of **1a** was obtained in the presence of the $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$/**B** (1:4) combination. With this system, a moderate erosion of the de values from 79 to 74% but a large increase in the catalyst turnover frequency from 2.5 to 360 h^{-1} was noticed upon increasing the reaction temperature from 20 to 80°C (entries 6–8). However, results of Table 1 clearly show that overexposure of the products under the reaction conditions causes a rapid decrease in chemoselectivity (mainly due to transesterification reactions) but also of the de values; on the other hand, only limited erosion of the ee ($\leq$2%) was observed. A possible reason for this phenomenon may arise from the use of a slight excess of base to generate the active species

from the in situ combination.[7] Recently, we have shown that side-reactions from 2-acylbenzoates could be overcome upon using the isolated active catalyst (1*S*,2*R*)-Ru **E** (Chart 1),[10] that allows us to perform selectively the transfer reduction under neutral conditions.[11] The application of this technique to the reduction of **1a** showed, as expected, a better resistance toward transesterification reactions, but de values still decreased, possibly because of the reversibility of the reaction (entry 13).[8] The reduction of *tert*-butyl (*R*)-6-benzyloxy-5-hydroxy-3-oxohexanoate (**1b**), an adequately substituted molecule for further functionalization,[1] proceeded in similar de for the *syn*-diol but was much faster and also more sensitive in terms of chemoselectivity.[†] No reaction was observed with *tert*-butyl (*R*)-6-chloro-5-hydroxy-3-oxohexanoate (**1c**), most likely because of catalyst poisoning by the chloro group as already observed with other chloro-containing substrates.[10]



(1*S*,2*R*)-Ru cat **E**

Chart 1.

In conclusion, transfer hydrogenation provides a promising catalytic alternative to traditional borane reagents for the *syn* diastereoselective reduction of chiral 5-hydroxy-3-ketoesters. Current investigations in this field are aimed at improving diastereoselectivities. New stereoselective catalytic routes toward functionalized-3,5-dihydroxyesters will be reported in due course.

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[†] In a typical experiment (entry 16), a solution of $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (6.2 mg, 0.01 mmol) and (1*S*,2*R*)-ephedrine (6.6 mg, 0.04 mmol) in dry freshly distilled 2-propanol (5 mL) was heated under nitrogen at 80°C for 20 min. After cooling the orange solution to room temperature, a solution of (*R*)-**1b** (615 mg, 2.0 mmol; 96% ee; prepared by aldolization of ethyl (*R*)-4-benzyloxy-3-hydroxybutyrate with AcO*t*Bu-LDA) in dry freshly distilled 2-propanol (14 mL) and 2-PrOK (1.0 mL, 0.12 m in 2-propanol, 0.12 mmol) were added. The resulting solution was placed in an oil bath at 30°C, stirred with a magnetic bar and the reaction was monitored by GLC analysis using a BPX5 capillary column. After evaporation of volatiles under vacuum the crude product was purified by column chromatography (silica, Et_2O–heptane) to provide **2b** as a pale yellow oil (370 mg, 61%). Full assignment of NMR resonances was made on the basis of $^1H,^1H$ COSY and $^{13}C,^1H$ HETCOR experiments; *syn*-(3*S*,5*R*)-**2b**: ^1H NMR ($CDCl_3$, 300 MHz): δ 7.31 (m, 5H, aro), 4.56 (s, 2H, PhCH_2), 4.34 (m, 1H, $CH_2CHOHCH_2$), 4.13 (m, 1H, OCH_2CHOH), 3.50 and 3.46 (2m, 2×1H, $PhCH_2OCH_2$), 2.45 and 2.37 (2m, 2×1H, J=6.3 Hz, CH_2CO_2), 2.01 and 1.50 (2m, 2×1H, $CHOHCH_2CHOH$), 1.44 (s, 9H, *t*Bu); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.46 (CO_2), 137.82, 127.89, 127.10 (aro), 80.03 (CMe_3), 73.08 (OCH_2CH), 72.87 ($PhCH_2$), 69.89 ($0CH_2CH$), 67.64 ($CHOHCH_2CO_2$), 42.99 (CH_2CO_2), 34.65 (OCH_2CH), 27.60 (CMe_3). *anti*-(3*R*,5*R*)-**2b** ^1H NMR: δ 7.33 (m, 5H), 4.56 (s, 2H), 4.27 (m, 1H), 4.12 (m, 1H), 3.49 (m, 2H), 2.43 (m, 2H), 1.60 (m, 2H), 1.46 (s, 9H); ^{13}C NMR: δ 171.98, 137.88, 128.27, 127.58, 81.01, 74.23, 73.20, 67.36, 65.26, 42.46, 38.77, 27.81. A small portion of the oily mixture containing diastereomers of **2b** (ca. 20 mg) was refluxed for 2 h in 2,2-dimethoxypropane (5 mL) in the presence of *para*-toluenesulfonic acid (2 mg); the corresponding acetonides[1] were analyzed by GLC on a BPX5 column (25 m×0.32 mm; 200°C, 0.2 bar N_2); the retention times for the *syn*- and *anti*-acetonides are t_R=11.38 and t_R=10.32 min, respectively.